Received: 25 December 2024 | Accepted: 25 April 2025

DOI: 10.1111/jog.16315

ORIGINAL ARTICLE

Ischemic placental disease as a risk factor for bronchopulmonary dysplasia in extremely preterm infants

Yu Ariyoshi[1] | Takayuki Iriyama[1] | Seisuke Sayama[1] | Eri Suzuki-Ariyoshi[1] | Eriko Yano[1] | Haruka Matsui[1] | Kensuke Suzuki[1] | Ayako Hashimoto[1] | Mari Ichinose[1] | Masatake Toshimitsu[1] | Takahiro Seyama[1] | Kenbun Sone[1] | Osamu Wada-Hiraike[1] | Atsushi Ito[2] | Yoshihiko Shitara[2] | Keiichi Kumasawa[1] | Akio Ishiguro[2] | Satsuki Kakiuchi[2] | Kohei Kashima[2] | Yasushi Hirota[1] | Naoto Takahashi[2] | Yutaka Osuga[1]

[1]Department of Obstetrics and Gynecology, Faculty of Medicine, The University of Tokyo, Tokyo, Japan

[2]Department of Pediatrics, Faculty of Medicine, The University of Tokyo, Tokyo, Japan

Correspondence
Takayuki Iriyama, Department of Obstetrics and Gynecology, Faculty of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan.
Email: iriyama-tky@umin.ac.jp

Abstract

Aim: This study aims to investigate the association between placental insufficiency and complications in extremely preterm infants in the context of ischemic placental disease (IPD), including preeclampsia, small-for-gestational-age (SGA), and placental abruption.

Methods: Infants born between 22 and 28 weeks of gestation were classified into IPD and non-IPD groups, matched 1:1 by gestational age and sex. The incidence of neonatal complications was analyzed.

Results: Analysis included 48 infants in each group. The IPD group had a significantly lower birth weight (IPD vs. non-IPD: 679 g vs. 979 g, $p < 0.001$), whereas the non-IPD group was characterized by a higher prevalence of spontaneous preterm births (12% vs. 79%, $p < 0.001$) and a significantly higher incidence of histological chorioamnionitis (CAM) (15% vs. 50%, $p < 0.001$). The IPD group showed a significantly higher incidence of bronchopulmonary dysplasia (BPD) compared to the non-IPD group (85% vs. 48%, $p < 0.001$), with no significant differences in other complications such as intraventricular hemorrhage, retinopathy of prematurity, and necrotizing enterocolitis. Logistic regression identified IPD as a significant risk factor for BPD (odds ratio [OR] [95% confidence interval]: 9.4 [2.8–31.8], $p < 0.001$), along with preeclampsia (OR: 4.9 [1.3–18.3], $p = 0.01$) and SGA (OR: 31.9 [5.9–171], $p < 0.001$). CAM was not associated with BPD (OR: 0.6 [0.2–1.7], $p = 0.45$).

Conclusions: Placental insufficiency, manifesting as IPD, is strongly associated with an increased risk of BPD in extremely preterm infants.

KEYWORDS
bronchopulmonary dysplasia, ischemic placental disease, placental insufficiency, preeclampsia, small-for-gestational-age

INTRODUCTION

Advances in perinatal and neonatal care have markedly improved the survival rates of extremely preterm infants.[1,2] However, these advancements are often accompanied by an increased risk of complications among survivors, particularly neurodevelopmental impairments, respiratory diseases, and gastrointestinal

disorders.[3–6] The current focus in perinatal medicine is to prioritize the prevention and management of postnatal complications, thereby ensuring that survivors can achieve long-term health and well-being. Achieving this goal requires the accurate identification of risk factors for complications in these infants and the provision of targeted interventions based on these risk profiles.

Recent research indicates that complications in preterm infants may not solely result from immaturity due to early gestational age but may also be influenced by underlying conditions that precipitate preterm birth.[7,8] Conditions leading to preterm delivery are generally classified into two primary groups: (1) those associated with intrauterine inflammation, often linked to chorioamnionitis (CAM) and resulting in spontaneous preterm birth, and (2) those related to placental abnormalities, leading to placental insufficiency, as observed in disorders such as preeclampsia (PE).[9] Numerous studies have demonstrated an association between intrauterine inflammation and complications in extremely preterm infants. Heightened inflammatory responses and immune activation during the fetal period, exemplified by fetal inflammatory response syndrome (FIRS), are recognized as significant contributors to long-term sequelae, including intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD), and neurodevelopmental impairments such as cerebral palsy.[10] Conversely, the impact of placental insufficiency, encompassing conditions like PE and small-for-gestational-age (SGA), on neonatal outcomes remains controversial. For instance, while some studies have reported an association between PE and the development of BPD,[11–13] others have found no such link.[14,15] These inconsistencies may stem from the diverse clinical manifestations of placental insufficiency, including PE, SGA, and placental abruption, as well as the significant overlap among these conditions.[16] This complexity complicates efforts to establish a definitive association between individual conditions and neonatal complications.

Recently, the novel disease concept of ischemic placental disease (IPD) has been introduced.[17–19] IPD encompasses conditions such as PE, SGA, and placental abruption, which share a common pathophysiological basis involving placental hypoxia and ischemia due to inadequate trophoblast invasion and suboptimal spiral artery remodeling during placentation. Despite its potential relevance, the association between IPD and complications in extremely preterm infants remains unexplored. Applying the IPD framework may enhance our understanding of the relationship between placental insufficiency and neonatal complications. Accordingly, this study aimed to investigate this association in extremely preterm infants within the context of IPD.

METHODS

This study was approved by the Institutional Review Board of the University of Tokyo (Approval Number: 2023275NI). Clinical data were collected from electronic medical records of mother-infant pairs born between 22 and 28 weeks of gestation at the University of Tokyo Hospital from 2011 to 2022. Exclusion criteria included intrauterine fetal death, multiple pregnancies, congenital malformations, chromosomal abnormalities, and congenital infections. This retrospective observational study was conducted using the opt-out method on the hospital website, following the guidance of the ethics committee and guidelines.

Active care in our hospital

As previously described,[20] in our tertiary care center, when delivery was anticipated after 22 0/7 weeks of gestation, parents were included in a shared decision-making process to determine preferences for active care. Active care encompassed obstetric and neonatal management strategies, including antenatal steroid administration, cesarean delivery, neonatal resuscitation, and respiratory support. Antenatal steroids were administered as two doses of 12 mg betamethasone given 24 h apart, ideally initiated after 22 0/7 weeks of gestation if delivery was expected within 1 week. Cesarean delivery was performed for fetal indications such as abnormal presentation, non-reassuring fetal status, suspected intraamniotic infection, or maternal conditions such as PE and placental abruption. For deliveries at 22 weeks of gestation, cesarean sections were performed following the shared decision-making process with parents and a thorough case-by-case assessment. Standard neonatal care included immediate intubation after delivery and surfactant administration shortly thereafter or upon arrival at the neonatal intensive care unit (NICU), as indicated. The treatment strategies for extremely preterm infants remained consistent at our institution over the past decade.

Definition of IPD

IPD was defined as the presence of one or more of the following complications: PE, SGA, or placental abruption. PE was defined according to criteria established by the International Society for the Study of Hypertension in Pregnancy.[21] SGA was classified as birth weight below the 10th percentile for gestational age based on Japanese growth charts.[22] Placental abruption was identified by the presence of a retroplacental hematoma observed at delivery.[23]

Maternal and fetal characteristics

Gestational age was determined based on the last menstrual period and confirmed by early pregnancy ultrasound. Umbilical arterial blood gas (ABG) samples were

collected from the clamped umbilical cord immediately after birth, and umbilical ABG pH was measured promptly. Spontaneous preterm birth was defined as preterm birth directly resulting from the spontaneous onset of preterm labor or preterm rupture of membranes. The delivered placenta underwent pathological examination, and histological CAM was assessed according to Blanc's classification,[24] focusing on Stage 2 or higher. Respiratory distress syndrome (RDS) was defined as cases requiring surfactant therapy based on a combination of clinical signs and x-ray findings. BPD was defined as the requirement for oxygen and/or mechanical ventilation or continuous positive airway pressure at 36 weeks postmenstrual age.[25] Mechanical ventilation duration was recorded. IVH and periventricular leukomalacia (PVL) were diagnosed using cranial ultrasound in the postnatal period and magnetic resonance imaging (MRI) at discharge.[26,27] IVH was defined as Grade 3 or higher, and PVL included both cystic and non-cystic forms. Necrotizing enterocolitis (NEC) was defined as Stage 2 or higher according to the Bell staging criteria.[28] Retinopathy of prematurity (ROP) was defined as cases requiring treatment, including anti-vascular endothelial growth factor (anti-VEGF) therapy or photocoagulation.[29]

Statistical analysis

The Mann–Whitney *U* test was applied to continuous variables, while Fisher's exact test was used for categorical variables. Continuous variables are presented as medians [interquartile range], and categorical variables are expressed as numbers (%). To account for the potential influence of gestational age and sex on complications, propensity score matching (PSM) was performed. Propensity scores were calculated using logistic regression with a caliper width of 0.2, followed by 1:1 nearest neighbor matching. After matching, the relationship between IPD and neonatal complications was analyzed. Kaplan–Meier curves were used to evaluate the duration of mechanical ventilation support, with differences assessed via the log-rank test. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated using Cox proportional hazards regression. Univariate analysis identified significant risk factors, which were further examined using logistic regression adjusted for gestational age, sex, and antenatal steroid to compute adjusted odds ratios (OR) with 95% CI. All statistical analyses were two-tailed, with a significance level of $p < 0.05$. Analyses were performed using GraphPad Prism version 9.5 (GraphPad Software, San Diego, CA, USA) and EZR, a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria).[30]

RESULTS

Figure 1a illustrates the study flowchart. A total of 145 mother-infant pairs satisfied the inclusion criteria,

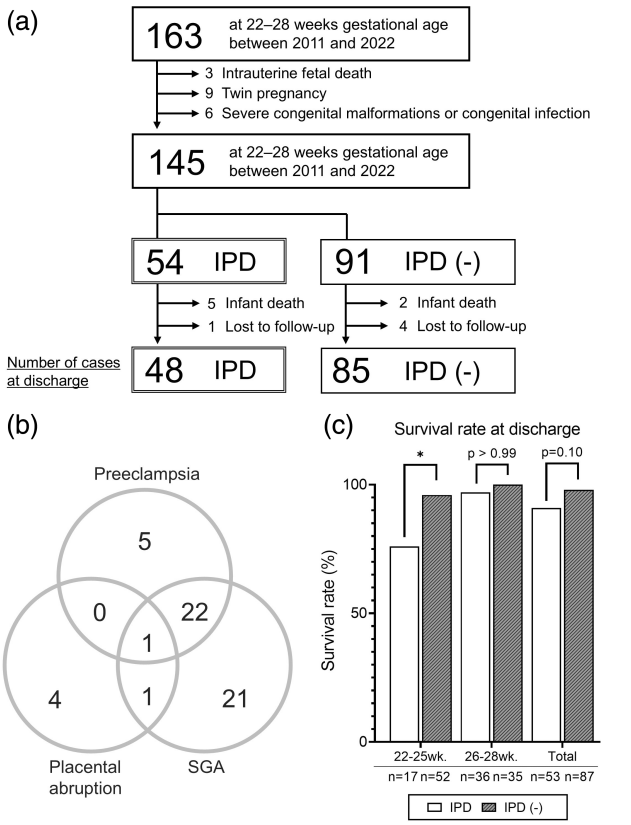

FIGURE 1 (a) Flow diagram depicting the details of the infants included in the study. (b) Venn diagram illustrating the conditions associated with ischemic placental disease (IPD), including preeclampsia, small-for-gestational-age (SGA), and placental abruption. Numbers in circles represent the number of cases for each condition, while overlapping areas indicate cases with multiple conditions. (c) Comparison of survival rates at discharge between the IPD and non-IPD groups. The analysis was performed for gestational age subgroups (22–25 weeks and 26–28 weeks), as well as the total cohort. The asterisk (*) indicates $p < 0.05$.

with all cases receiving active care during the study period. The IPD group consisted of 54 cases, while the non-IPD group included 91 cases. The follow-up rate until NICU discharge was 140/145 (97%), and the survival rate was 138/145 (95%). Among the IPD group, 24/54 (44%) exhibited two or more of the following conditions: PE, SGA, and placental abruption (Figure 1b). Notably, 23/28 (82%) of PE cases were also diagnosed with SGA. The survival rate at discharge was 48/53 (91%) in the IPD group and 85/87 (98%) in the non-IPD group, with no statistically significant difference between the groups. Among the five cases that died in the IPD group, two involved placental abruption, one had SGA, and two presented with both PE and SGA. Subgroup analysis based on gestational age revealed that the discharge survival rate for infants born at 22–25 weeks of gestation was 13/17 (76%) in the IPD group, compared to 50/52 (96%) in the non-IPD group, indicating a significantly lower survival rate in the IPD group (Figure 1c).

TABLE 1 Comparison of maternal and infant characteristics between the ischemic placental disease (IPD) and non-IPD groups.

	Number (%)							
			Before matching			After matching		
	IPD	*n*	IPD (−)	*n*	*p*	Matched IPD (−)	*n*	*p*
Maternal age / Median (IQR) (years)	36.5 (33–39)	48	35 (32–39)	85	0.22	36 (32–39)	48	0.40
Body mass index >25	7 (15)	48	11 (12)	85	0.79	6 (13)	48	>0.99
Assisted reproductive technology	12 (25)	48	24 (28)	85	0.83	16 (33)	48	0.50
Multiparous	19 (40)	48	32 (38)	85	0.85	16 (33)	48	0.67
Smoking history	3 (6.2)	48	6 (7.1)	85	>0.99	3 (6.2)	48	>0.99
Antenatal steroid	43 (90)	48	62 (73)	85	0.02	33 (69)	48	0.02
Spontaneous preterm birth	6 (12)	48	73 (86)	85	<0.001	38 (79)	48	<0.001
Histological chorioamnionitis	7 (15)	48	48 (56)	85	<0.001	24 (50)	48	<0.001
Sex (male)	26 (54)	48	41 (48)	85	0.59	25 (52)	48	>0.99
Gestational age Median (IQR) (weeks)	26.9 (25.9–27.9)	48	25.4 (23.6–27.0)	85	<0.001	26.9 (25.7–27.9)	48	0.99
Birth weight Median (IQR) (g)	679 (519–792)	48	769 (599–999)	85	0.002	979 (768–1113)	48	<0.001
Birth weight <500 g	11 (23)	48	4 (4.7)	85	0.003	0 (0)	48	<0.001
Cesarean section	47 (98)	48	72 (85)	85	0.02	40 (83)	48	0.03
5 min Apgar score<7	11 (23)	48	37 (44)	84	0.001	21 (45)	47	0.03
Umbilical ABG pH <7.1	7 (17)	42	6 (8.7)	69	0.23	4 (11)	38	0.52

Abbreviations: ABG, arterial blood gas; IQR, interquartile range.

Table 1 presents a comparison of maternal and neonatal background factors between the IPD and non-IPD groups. No significant differences were observed in maternal characteristics. However, antenatal steroid use and cesarean section rates were significantly higher in the IPD group than in the non-IPD group. The IPD group also exhibited a significantly greater gestational age (26.9 vs. 25.4 weeks, $p < 0.001$) and a significantly lower birth weight (679 vs. 769 g, $p = 0.002$). Furthermore, in the IPD group, 11/48 (23%) of cases had a birth weight below 500 g, compared to 4/85 (4.7%) in the non-IPD group ($p < 0.001$). Among the non-IPD group, 73/85 (86%) cases were attributed to spontaneous preterm birth, compared to 6/48 (12%) in the IPD group. Additionally, the IPD group demonstrated a significantly lower incidence of CAM (15% vs. 56%, $p < 0.001$). Considering that gestational age and sex influence postnatal complications,[8,31] PSM was applied to adjust for these factors, resulting in 1:1 matching. Following matching, 48 cases in the IPD group and 48 in the non-IPD group were compared. The IPD group retained a significantly lower birth weight (679 vs. 979 g, $p < 0.001$), while the non-IPD group maintained a significantly higher incidence of CAM (15% vs. 50%, $p < 0.001$). Table 2 compares neonatal complication rates between the IPD and non-IPD groups after matching. The IPD group demonstrated a significantly higher incidence of BPD compared to the non-IPD group (85% vs. 48%, $p < 0.001$). No significant differences were observed for other complications, including IVH, NEC, and ROP. To further evaluate the impact of IPD on respiratory outcomes, the duration of mechanical ventilation support was analyzed (Figure 2). The analysis revealed that the duration of mechanical ventilation support was significantly longer in the IPD group than in the non-IPD group (HR [95% CI]: 2.3 [1.5–3.6], $p < 0.001$).

Additionally, logistic regression analyses were conducted to evaluate the impacts of IPD (including its components: PE, SGA, and placental abruption) and CAM on BPD, with each factor individually adjusted for gestational age and sex. These analyses utilized a total of 133 cases (48 from the IPD group and 85 from the non-IPD group), representing the study population prior to PSM (Table 3). The analyses demonstrated that IPD was significantly associated with the development of BPD (OR [95% CI]: 9.4 [2.8–31.8], $p < 0.001$). In contrast, CAM was not associated with BPD incidence (OR: 0.6 [0.2–1.7], $p = 0.45$). Furthermore, SGA (OR: 31.9 [5.9–171], $p < 0.001$) and PE (OR: 4.9 [1.3–18.3], $p = 0.01$) were identified as significant risk factors for BPD development.

DISCUSSION

The present study examined the association between placental insufficiency, manifesting as IPD, and adverse outcomes in extremely preterm infants. Infants born to

TABLE 2 Comparison of infant complications between the ischemic placental disease (IPD) and non-IPD groups.

	Number (%)				
	IPD	***n***	**Matched IPD (−)**	***n***	***p***
Respiratory distress syndrome	42 (88)	48	42 (88)	48	>0.99
Bronchopulmonary dysplasia	41 (85)	48	23 (48)	48	<0.001
Intraventricular hemorrhage	2 (4.2)	48	2 (4.2)	48	>0.99
Periventricular leukomalacia	1 (2.1)	48	3 (6.2)	48	0.62
Necrotizing enterocolitis	2 (4.2)	48	2 (4.2)	48	>0.99
Retinopathy of prematurity	20 (42)	48	12 (25)	48	0.13

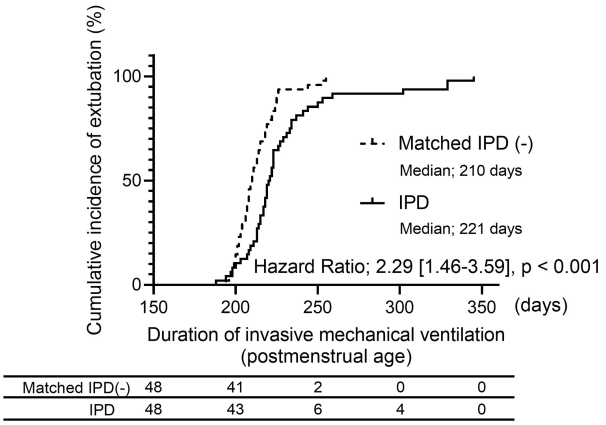

FIGURE 2 Comparison of cumulative incidence of extubation between the ischemic placental disease (IPD) and matched non-IPD groups. Kaplan–Meier curves show the proportion of infants still on mechanical ventilation. The table below the graph lists the number of infants still on mechanical ventilation at specific time points.

mothers with IPD demonstrated a significantly increased incidence of BPD and required prolonged mechanical ventilation. Additionally, infants born to mothers with IPD at 22–25 weeks of gestation exhibited significantly lower survival rates. These findings underscore the crucial role of placental insufficiency as a prenatal risk factor contributing to both mortality and morbidity in extremely preterm infants.

PE, SGA, and placental abruption are conditions associated with placental insufficiency, characterized by placental ischemia and chronic hypoxia due to inadequate uteroplacental blood flow. These conditions account for over 50% of medically indicated preterm births.[18] Collectively defined as IPD, these conditions have gained increasing attention in recent years. While previous studies have investigated the relationship between individual conditions and outcomes in preterm infants, none have examined this from the broader perspective of IPD, which comprehensively captures abnormalities resulting from placental insufficiency. In preterm births, conditions such as PE, SGA, and placental abruption frequently coexist.[16] In this study, 44% of patients in the IPD group exhibited two or more of these conditions. These findings demonstrate that disorders related to placental insufficiency are closely interconnected in the context of extremely preterm birth, emphasizing the importance of evaluating neonatal outcomes within the framework of IPD.

The present study demonstrated that the IPD group, characterized by placental insufficiency, exhibited a stronger association with BPD compared to the non-IPD group, which predominantly consisted of spontaneous preterm births often associated with CAM. BPD has traditionally been considered a condition primarily induced by lung injury due to excessive mechanical ventilation and high oxygen exposure following birth.[32] However, with advances in perinatal care, prenatal risk factors have garnered increasing attention, and CAM has been widely recognized as a significant contributor to the development of BPD.[33] In contrast, recent studies have increasingly highlighted the association between placental insufficiency, particularly SGA, and the development of BPD.[34] While the role of PE in the incidence of BPD remains debated,[11–15] it has been identified as a risk factor when accompanied by fetal growth restriction.[35] In the present study, PE was observed in 82% of cases with SGA, suggesting that the coexistence of PE and SGA may compound the risk of BPD. A key finding of our study is that our multivariate analysis revealed a stronger association between placental insufficiency and the development of BPD in extremely preterm infants, when compared to CAM.

Few studies have compared the risks of complications in preterm infants related to placental insufficiency and CAM in spontaneous preterm birth. One prospective study examined neonatal complications in two groups of preterm infants born between 23 and 31 weeks: one group with mothers who had hypertensive disorders of pregnancy or SGA, and another with mothers who delivered due to preterm premature rupture of membranes or spontaneous preterm labor.[8] The study found that the former group had a higher risk of BPD and ROP, while the latter group had a higher risk of IVH. These findings suggest that placental insufficiency is indeed a risk factor for BPD, aligning with the results of our study. However, the previous study did not specify the proportion of CAM in spontaneous preterm births, nor did it include histological evaluation of the placenta. By addressing

TABLE 3 Logistic regression analysis of factors contributing to the development of bronchopulmonary dysplasia.

	Unadjusted			Adjusted[a]		
	OR	95% CI	*p*	OR	95% CI	*p*
IPD	3.2	1.3–8.0	0.01	9.4	2.8–31.8	<0.001
Preeclampsia	2.5	0.8–7.7	0.12	4.9	1.3–18.3	0.01
SGA	12.0	2.7–52.7	0.001	31.9	5.9–171	<0.001
Placental abruption	1.2	0.1–11.5	0.90	2.6	0.1–41.1	0.49
Histological chorioamnionitis	1.2	0.6–2.7	0.61	0.6	0.2–1.7	0.45

Abbreviations: CI, confidence intervals; IPD, ischemic placental disease; OR, odds ratios; SGA, small-for-gestational-age.
[a]Adjustments were made for gestational age, infant gender, and antenatal steroid for each factor.

these gaps, our study further underscores the importance of placental insufficiency as a risk factor for BPD, particularly in comparison with CAM.

It is generally accepted that inflammation resulting from CAM triggers a systemic inflammatory response in the fetus, thereby increasing the risk of neonatal complications, including BPD.[36] In our study, the number of clinical CAM cases, diagnosed based on the presence of maternal fever accompanied by other symptoms, such as elevated white blood cell count,[37] was small, with only 8 out of 133 cases (6.0%). As part of our management protocol, especially in cases of preterm premature rupture of membranes, we administer steroids and aim for early delivery before clinical infection can develop. We hypothesize that most cases underwent cesarean section before clinical CAM could manifest, thus potentially minimizing the infection's impact on the fetus. Additionally, it is well established that lower birth weight, which leads to a higher proportion of SGA in the cohort, increases the risk of BPD.[34] In our study, 11% of the infants weighed less than 500 g at birth. Similarly, a study in which 12% of infants weighed less than 500 g at birth also reported that CAM was not a significant risk factor for BPD.[38] Therefore, in cohorts with a higher proportion of infants with low birth weights, birth weight itself is a dominant risk factor for BPD, which may have attenuated the relative impact of CAM.

Recent studies suggest that while antenatal steroids reduce the incidence of RDS, they may increase the risk of BPD, particularly when birth occurs more than 7 days after steroid administration.[39–42] In this study, 11/43 (25%) of the IPD group and 15/62 (24%) of the non-IPD group had a ≥7-day interval between steroid administration and birth, without a significant difference. Even after adjusting for covariates including antenatal steroid, IPD remained a significant risk factor for BPD whereas CAM was not identified as one.

This study has several limitations. As a small-scale retrospective cohort study, the limited number of placental abruption cases may have constrained our ability to comprehensively evaluate its potential association with neonatal complications. Additionally, the low incidence of other complications, such as NEC, IVH, and PVL, resulted in insufficient sample sizes for robust analysis, highlighting the need for further research. However, the consistency of perinatal care policies in this single-center study over the past decade constitutes a strength. In many countries, the provision of active care for infants born at 22–23 weeks of gestation remains a subject of debate due to concerns over potential long-term complications.[43,44] At our institution, active care is provided while respecting patient autonomy. Consequently, the findings of this study may not be directly applicable to other countries or regions.

In conclusion, this study demonstrated that placental insufficiency, as conceptualized through IPD, is a crucial factor contributing to the increased risk of BPD in extremely preterm infants, underscoring its significant impact on neonatal outcomes.

AUTHOR CONTRIBUTIONS

Yu Ariyoshi: Conceptualization; methodology; writing – original draft. **Takayuki Iriyama:** Conceptualization; methodology; writing – original draft. **Seisuke Sayama:** Formal analysis; methodology; writing – review and editing. **Eri Suzuki-Ariyoshi:** Formal analysis; methodology; writing – review and editing. **Eriko Yano:** Formal analysis; methodology; writing – review and editing. **Haruka Matsui:** Formal analysis; methodology; writing – review and editing. **Kensuke Suzuki:** Formal analysis; methodology; writing – review and editing. **Ayako Hashimoto:** Formal analysis; methodology; writing – review and editing. **Mari Ichinose:** Formal analysis; methodology; writing – review and editing. **Masatake Toshimitsu:** Formal analysis; methodology; writing – review and editing. **Takahiro Seyama:** Formal analysis; methodology; writing – review and editing. **Kenbun Sone:** Formal analysis; methodology; writing – review and editing. **Osamu Wada-Hiraike:** Formal analysis; methodology; writing – review and editing. **Atsushi Ito:** Formal analysis; methodology; writing – review and editing. **Yoshihiko Shitara:** Formal analysis; methodology; writing – review and editing. **Keiichi Kumasawa:** Formal analysis; methodology; writing – review and editing. **Akio Ishiguro:** Formal analysis; methodology; writing – review and editing. **Satsuki Kakiuchi:** Formal analysis; methodology; writing – review and editing. **Kohei Kashima:** Formal analysis; methodology;

writing – review and editing. **Yasushi Hirota:** Supervision. **Naoto Takahashi:** Supervision. **Yutaka Osuga:** Supervision.

CONFLICT OF INTEREST STATEMENT

Takayuki Iriyama is an Editorial Board member of JOG Journal and the corresponding author of this article. To minimize bias, they were excluded from all editorial decision-making related to the acceptance of this article for publication.

DATA AVAILABILITY STATEMENT

The data are not publicly available due to ethical restrictions. Disclosure of the patients' data via a public repository was not included in the study protocol, on which the institutional review board's approval was acquired.

ETHICS STATEMENT

All methods used in this study were conducted in accordance with the relevant guidelines and regulations and were approved by the Institutional Review Board at the University of Tokyo (Approval Number: 2023275NI). This retrospective observational study was conducted using the opt-out method on our hospital website, as per the guidance of the ethics committee and guidelines.

ORCID

Takayuki Iriyama https://orcid.org/0000-0001-7970-6695
Mari Ichinose https://orcid.org/0000-0002-2974-9109
Masatake Toshimitsu https://orcid.org/0000-0002-0509-7812
Osamu Wada-Hiraike https://orcid.org/0000-0002-3458-6711
Keiichi Kumasawa https://orcid.org/0000-0003-0865-604X
Yutaka Osuga https://orcid.org/0000-0002-6660-1066

REFERENCES

1. Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S, et al. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993–2012. JAMA. 2015; 314:1039–51.
2. Patel RM, Kandefer S, Walsh MC, Bell EF, Carlo WA, Laptook AR, et al. Causes and timing of death in extremely premature infants from 2000 through 2011. N Engl J Med. 2015; 372(4):331–40. https://doi.org/10.1056/NEJMoa1403489
3. Ward RM, Beachy JC. Neonatal complications following preterm birth. BJOG. 2003;110(Suppl 20):8–16.
4. Rattihalli RR, Lamming CR, Dorling J, Manktelow BN, Bohin S, Field DJ, et al. Neonatal intensive care outcomes and resource utilisation of infants born <26 weeks in the former Trent region: 2001–2003 compared with 1991–1993. Arch Dis Child Fetal Neonatal Ed. 2011;96:F329–34.
5. Bell EF, Hintz SR, Hansen NI, Bann CM, Wyckoff MH, DeMauro SB, et al. Mortality, in-hospital morbidity, care practices, and 2-year outcomes for extremely preterm infants in the US, 2013–2018. JAMA. 2022;327:248–63.
6. Lui K, Lee SK, Kusuda S, Adams M, Vento M, Reichman B, et al. Trends in outcomes for neonates born very preterm and very low birth weight in 11 high-income countries. J Pediatr. 2019;215: 32.e14–40.e14.
7. Basso O, Wilcox A. Mortality risk among preterm babies: immaturity versus underlying pathology. Epidemiology. 2010; 21:521–7.
8. Gagliardi L, Rusconi F, Da Frè M, Mello G, Carnielli V, Di Lallo D, et al. Pregnancy disorders leading to very preterm birth influence neonatal outcomes: results of the population-based ACTION cohort study. Pediatr Res. 2013;73:794–801.
9. McElrath TF, Hecht JL, Dammann O, Boggess K, Onderdonk A, Markenson G, et al. Pregnancy disorders that lead to delivery before the 28th week of gestation: an epidemiologic approach to classification. Am J Epidemiol. 2008;168:980–9. https://doi.org/10.1093/aje/kwn202
10. Jung E, Romero R, Yeo L, Diaz-Primera R, Marin-Concha J, Para R, et al. The fetal inflammatory response syndrome: the origins of a concept, pathophysiology, diagnosis, and obstetrical implications. Semin Fetal Neonatal Med. 2020;25:101146.
11. Hansen AR, Barnés CM, Folkman J, McElrath TF. Maternal preeclampsia predicts the development of bronchopulmonary dysplasia. J Pediatr. 2010;156:532–6.
12. Rocha G, de Lima FF, Machado AP, Guimarães H, Collaborators of the Hypertensive Disorders of Pregnancy Study Group. Preeclampsia predicts higher incidence of bronchopulmonary dysplasia. J Perinatol. 2018;38(9):1165–73. https://doi.org/10.1038/s41372-018-0133-8
13. Durrmeyer X, Kayem G, Sinico M, Dassieu G, Danan C, Decobert F. Perinatal risk factors for bronchopulmonary dysplasia in extremely low gestational age infants: a pregnancy disorder-based approach. J Pediatr. 2012;160:578–583.e2.
14. O'Shea JE, Davis PG, Doyle LW, Victorian Infant Collaborative Study Group. Maternal preeclampsia and risk of bronchopulmonary dysplasia in preterm infants. Pediatr Res. 2012;71(2):210–4. https://doi.org/10.1038/pr.2011.27
15. Soliman N, Chaput K, Alshaikh B, Yusuf K. Preeclampsia and the risk of bronchopulmonary dysplasia in preterm infants less than 32 weeks' gestation. Am J Perinatol. 2017;34:585–92.
16. Ananth CV, Smulian JC, Vintzileos AM. Ischemic placental disease: maternal versus fetal clinical presentations by gestational age. J Matern Fetal Neonatal Med. 2010;23:887–93.
17. Di Renzo GC. The great obstetrical syndromes. J Matern Fetal Neonatal Med. 2009;22:633–5.
18. Ananth CV, Vintzileos AM. Maternal-fetal conditions necessitating a medical intervention resulting in preterm birth. Am J Obstet Gynecol. 2006;195:1557–63.
19. Ananth CV, Friedman AM. Ischemic placental disease and risks of perinatal mortality and morbidity and neurodevelopmental outcomes. Semin Perinatol. 2014;38:151–8.
20. Ariyoshi Y, Iriyama T, Seyama T, Sayama S, Yano E, Suzuki K, et al. Neurological outcomes and associated perinatal factors in infants born between 22 and 25 weeks with active care. J Perinatol. 2025;45:186–93.
21. Magee LA, Brown MA, Hall DR, Gupte S, Hennessy A, Karumanchi SA, et al. The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis & management recommendations for international practice. Pregnancy Hypertens. 2022;27:148–69.
22. Itabashi K, Miura F, Uehara R, Nakamura Y. New Japanese neonatal anthropometric charts for gestational age at birth. Pediatr Int. 2014;56:702–8.
23. Elsasser DA, Ananth CV, Prasad V, Vintzileos AM, New Jersey-Placental Abruption Study Investigators. Diagnosis of placental abruption: relationship between clinical and histopathological findings. Eur J Obstet Gynecol Reprod Biol. 2010;148(2):125–30. https://doi.org/10.1016/j.ejogrb.2009.10.005
24. Blanc WA. Pathology of the placenta, membranes, and umbilical cord in bacterial, fungal, and viral infections in man. Monogr Pathol. 1981;22:67–132.

25. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2001;163(7):1723–9. https://doi.org/10.1164/ajrccm.163.7.2011060
26. Novak CM, Ozen M, Burd I. Perinatal brain injury: mechanisms, prevention, and outcomes. Clin Perinatol. 2018;45(2):357–75. https://doi.org/10.1016/j.clp.2018.01.015
27. Reddy N, Doyle M, Hanagandi P, Taranath A, Dahmoush H, Krishnan P, et al. Neuroradiological mimics of periventricular leukomalacia. J Child Neurol. 2022;37:151–67.
28. Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg. 1978;187:1–7.
29. Sabri K, Ells AL, Lee EY, Dutta S, Vinekar A. Retinopathy of prematurity: a global perspective and recent developments. Pediatrics. 2022;150:e2021053924.
30. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013;48:452–8.
31. Klinger G, Sokolover N, Boyko V, Sirota L, Lerner-Geva L, Reichman B, et al. Perinatal risk factors for bronchopulmonary dysplasia in a national cohort of very-low-birthweight infants. Am J Obstet Gynecol. 2013;208:115.e1–115.e9.
32. Northway WH Jr, Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. N Engl J Med. 1967;276(7):357–68. https://doi.org/10.1056/NEJM196702162760701
33. Hartling L, Liang Y, Lacaze-Masmonteil T. Chorioamnionitis as a risk factor for bronchopulmonary dysplasia: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed. 2012;97:F8–F17.
34. Zeitlin J, El Ayoubi M, Jarreau PH, Draper ES, Blondel B, Künzel W, et al. Impact of fetal growth restriction on mortality and morbidity in a very preterm birth cohort. J Pediatr. 2010;157(733–739):733.e1–739.e1.
35. Bose C, Van Marter LJ, Laughon M, O'Shea TM, Allred EN, Karna P, et al. Fetal growth restriction and chronic lung disease among infants born before the 28th week of gestation. Pediatrics. 2009;124:e450–8.
36. Romero R, Gotsch F, Pineles B, Kusanovic JP. Inflammation in pregnancy: its roles in reproductive physiology, obstetrical complications, and fetal injury. Nutr Rev. 2007;65:S194–202.
37. Lencki SG, Maciulla MB, Eglinton GS. Maternal and umbilical cord serum interleukin levels in preterm labor with clinical chorioamnionitis. Am J Obstet Gynecol. 1994;170:1345–51.
38. Pappas A, Kendrick DE, Shankaran S, Stoll BJ, Bell EF, Laptook AR, et al. Chorioamnionitis and early childhood outcomes among extremely low-gestational-age neonates. JAMA Pediatr. 2014;168:137–47.
39. Ushida T, Kotani T, Hayakawa M, Hirakawa A, Sadachi R, Nakamura N, et al. Antenatal corticosteroids and preterm offspring outcomes in hypertensive disorders of pregnancy: a Japanese cohort study. Sci Rep. 2020;10:9312.
40. Sasaki Y, Ikeda T, Nishimura K, Katsuragi S, Sengoku K, Kusuda S, et al. Association of antenatal corticosteroids and the mode of delivery with the mortality and morbidity of infants weighing less than 1,500 g at birth in Japan. Neonatology. 2014;106:81–6.
41. Chen F, Bajwa NM, Rimensberger PC, Posfay-Barbe KM, Pfister RE, Swiss Neonatal Network. Thirteen-year mortality and morbidity in preterm infants in Switzerland. Arch Dis Child Fetal Neonatal Ed. 2016;101:F377–83.
42. Fuma K, Kotani T, Tsuda H, Oshiro M, Tano S, Ushida T, et al. Impact of antenatal corticosteroids-to-delivery interval on very preterm neonatal outcomes: a retrospective study in two tertiary centers in Japan. BMC Pregnancy Childbirth. 2024;18(24):607.
43. Isayama T, Miyakoshi K, Namba F, Hida M, Morioka I, Ishii K, et al. Survival and unique clinical practices of extremely preterm infants born at 22–23 weeks' gestation in Japan: a national survey. Arch Dis Child Fetal Neonatal Ed. 2025;110(1):17–22. https://doi.org/10.1136/archdischild-2023-326355
44. Guillén Ú, Weiss EM, Munson D, Maton P, Jefferies A, Norman M, et al. Guidelines for the management of extremely premature deliveries: a systematic review. Pediatrics. 2015;136:343–50.

How to cite this article: Ariyoshi Y, Iriyama T, Sayama S, Suzuki-Ariyoshi E, Yano E, Matsui H, et al. Ischemic placental disease as a risk factor for bronchopulmonary dysplasia in extremely preterm infants. J Obstet Gynaecol Res. 2025;51(5):e16315. https://doi.org/10.1111/jog.16315